

## Partial pneumonectomy of telomerase null mice carrying shortened telomeres initiates cell growth arrest resulting in a limited compensatory growth response.

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### Public Summary:

Telomerase mutations and significantly shortened chromosomal telomeres have recently been implicated in human lung pathologies. Natural telomere shortening is an inevitable consequence of aging, which is also a risk factor for development of lung disease. However, the impact of shortened telomeres and telomerase dysfunction on the ability of lung cells to respond to significant challenge is still largely unknown. We have previously shown that lungs of late generation, telomerase null B6.Cg-Terc(tm1Rdp) mice feature alveolar simplification and chronic stress signaling at baseline, a phenocopy of aged lung. To determine the role telomerase plays when the lung is challenged, B6.Cg-Terc(tm1Rdp) mice carrying shortened telomeres and wild-type controls were subjected to partial pneumonectomy. We found that telomerase activity was strongly induced in alveolar epithelial type 2 cells (AEC2) of the remaining lung immediately following surgery. Eighty-six percent of wild-type animals survived the procedure and exhibited a burst of early compensatory growth marked by upregulation of proliferation, stress response, and DNA repair pathways in AEC2. In B6.Cg-Terc(tm1Rdp) mice carrying shortened telomeres, response to pneumonectomy was characterized by decreased survival, diminished compensatory lung growth, attenuated distal lung progenitor cell response, persistent DNA damage, and cell growth arrest. Overall, survival correlated strongly with telomere length. We conclude that functional telomerase and properly maintained telomeres play key roles in both long-term survival and the early phase of compensatory lung growth following partial pneumonectomy.

### Scientific Abstract:

Telomerase mutations and significantly shortened chromosomal telomeres have recently been implicated in human lung pathologies. Natural telomere shortening is an inevitable consequence of aging, which is also a risk factor for development of lung disease. However, the impact of shortened telomeres and telomerase dysfunction on the ability of lung cells to respond to insult and mount effective repair is still largely unknown. We have previously shown that lungs of late generation, telomerase null B6.Cg-Terc(tm1Rdp) mice feature alveolar simplification and chronic stress signaling at baseline, a phenocopy of aged lung. To determine the role telomerase plays in response to lung injury, B6.Cg-Terc(tm1Rdp) mice carrying shortened telomeres and wild type controls were subjected to partial pneumonectomy. We found that telomerase activity was strongly induced alveolar epithelial type 2 cells (AEC2) of the remaining lung immediately following surgery. 86% of wild type animals survived the procedure and exhibited a burst of early compensatory growth marked by upregulation of proliferation, stress response and DNA repair pathways in AEC2. In B6.Cg-Terc(tm1Rdp) mice carrying shortened telomeres, response to pneumonectomy was characterized by decreased survival, diminished compensatory lung growth, attenuated distal lung progenitor cell response, persistent DNA damage and cell growth arrest. Over all, survival correlated strongly with telomere length. We conclude that functional telomerase and properly maintained telomeres play key roles in both long term survival and the early phase of compensatory lung growth following partial pneumonectomy.

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